

REMARKS

The amendments to the claims are to matters of form directed to bringing the claims in conformance with U.S. patent practice. The claims were not narrowed by these amendments. As such, these amendments raise no issue of new matter and Applicants respectfully request their entry.

If there is any fee due in connection with the filing of this Preliminary Amendment, please charge the fee to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

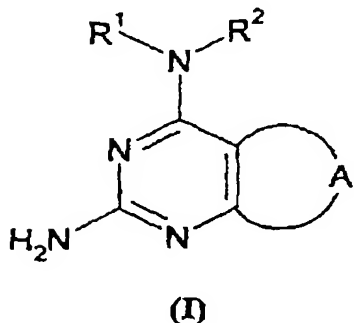
Dated: March 12, 2002

By: 

Anthony C. Tridico
Reg. No. 45,958

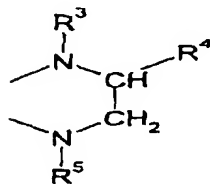
APPENDIX TO THE PRELIMINARY AMENDMENT

1. (Amended) A compound of [Compounds of the] formula I

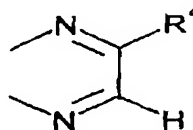


in which

A is [a bridge of the formula]



or



R^1 is hydrogen, C_1 - C_{20} -alkyl, C_2 - C_{20} -alkenyl, C_2 - C_{20} -alkynyl, cycloalkyl with three to eight ring carbon atoms, cycloalkenyl with three to eight ring carbon atoms, cycloalkylalkyl with five to six ring carbon atoms, aryl, alkylaryl or arylalkyl, wherein R^1 is unsubstituted or substituted with at least one substituent chosen from R^6 [where the organic radicals may be substituted by one or more substituents R^6],

R^2 is [, independently of R^1 ,] C_1 - C_{20} -alkyl, C_2 - C_{20} -alkenyl, C_2 - C_{20} -alkynyl, cycloalkyl with three to eight ring carbon atoms, cycloalkenyl with three to eight ring carbon atoms, cycloalkylalkyl with five to six ring carbon atoms, aryl, alkylaryl or arylalkyl, wherein R^2 is unsubstituted or substituted with at least one substituent chosen from R^6 [where the organic radicals may be substituted by one or more substituents R^6],

or R^1 and R^2 [may], together with the nitrogen atom bearing them, form a 3-8-membered ring, wherein said 3-8-membered ring optionally comprises [which may optionally contain] 0, 1 or 2 further heteroatoms chosen from [the series] N, O, and S_1 and [which is optionally substituted by one or more radicals] wherein said 3-8-membered ring is unsubstituted or substituted by at least one radical,

R^3 is hydrogen, -CO-alkyl, -CO-alkylaryl or -CO-aryl,

R^4 is C_1 - C_{20} -alkyl, C_2 - C_{20} -alkenyl, C_2 - C_{20} -alkynyl, cycloalkyl with three to eight ring carbon atoms, cycloalkenyl with three to eight ring carbon atoms, cycloalkylalkyl with five to six ring carbon atoms, aryl, [or] alkylaryl, arylalkyl, -CO-O-alkyl, -CO-O-aryl, -CO-alkyl -CO-aryl, [where the organic radicals may be substituted by one or more substituents R^7] **wherein R^4 is unsubstituted or substituted with at least one substituent chosen from R^7 ,**

R^5 is[, independently of R^3 ,] hydrogen, -CO-alkyl, -CO-alkylaryl or -CO-aryl,

R^6 is -F, -OH, -O-(C_1 - C_{10})-alkyl, -O-phenyl, -O-CO-(C_1 - C_{10})-alkyl, -O-CO-aryl, - NR^8R^9 , oxo, phenyl, -CO-(C_1 - C_5)-alkyl, - CF_3 , -CN, -CONR⁸R⁹, -COOH, -CO-O-(C_1 - C_5)-alkyl, -CO-O-aryl, -S(O)_n-(C_1 - C_5)-alkyl, **or** -SO₂-NR⁸R⁹,

R^7 [has, independently of R^6 , one of the meanings of R^6 ,] **is -F, -OH, -O-(C_1 - C_{10})-alkyl, -O-phenyl, -O-CO-(C_1 - C_{10})-alkyl, -O-CO-aryl, - NR^8R^9 , oxo, phenyl, -CO-(C_1 - C_5)-alkyl, - CF_3 , -CN, -CONR⁸R⁹, -COOH, -CO-O-(C_1 - C_5)-alkyl, -CO-O-aryl, -S(O)_n-(C_1 - C_5)-alkyl, or -SO₂-NR⁸R⁹,**

R^8 is hydrogen or C_1 - C_{20} -alkyl, **and**

R^9 is hydrogen, C_1 - C_{20} -alkyl or aryl,

or a physiologically acceptable salt, hydrate, or ester thereof, in any stereoisomeric or tautomeric form, or a mixture of any such compounds in any ratio. [in all its stereoisomeric and tautomeric forms and mixtures thereof in all ratios, and its physiologically acceptable salts, hydrates and esters.]

2. (Amended) **The compound as claimed in claim 1** [Compounds of the formula I as claimed in claim 1], in which

R^1 is hydrogen, (C_1 - C_{10})-alkyl, (C_3 - C_8)-cycloalkyl, cycloalkylalkyl, aryl [or] (C_1 - C_3)-alkylaryl or arylalkyl, [where the alkyl radicals may be substituted by one or more substituents R^6 ,] **wherein R^1 is unsubstituted or the alkyl radicals are substituted with at least one substituent chosen from R^6**

R^2 is[, independently of R^1 ,] (C_1 - C_{10})-alkyl, (C_3 - C_8)-cycloalkyl, cycloalkylalkyl, aryl or (C_1 - C_3)-alkylaryl, [where the alkyl radicals may be substituted by one or more substituents R^6 ,] **wherein R^2 is unsubstituted or the alkyl radicals are substituted with at least one substituent chosen from R^6**

or R^1 and R^2 [may], together with the nitrogen atom bearing them, form a 3-8-membered ring, **wherein said 3-8-membered ring optionally comprises** [which may optionally contain] 0, 1 or 2 further heteroatoms **chosen** from [the series] N, O, **and** S and [which is optionally substituted by one or more radicals] **and wherein said 3-8-membered ring is unsubstituted or substituted by at least one radical,**

R^3 is hydrogen, -CO-(C_1 - C_7)-alkyl, -CO-(C_1 - C_3)-alkylaryl or -CO-aryl,

R^4 is (C_1 - C_{10})-alkyl, aryl [or] (C_1 - C_3)-alkylaryl, -CO-O-(C_1 - C_5)-alkyl, -CO-O-aryl, -CO-(C_1 - C_5)-alkyl or -CO-aryl, [where the alkyl radicals may be substituted by one or more substituents R^7 ,] **wherein R^4 is unsubstituted or the alkyl radicals are substituted with at least one substituent chosen from R^7**

R⁵ [has, independently of R³, one of the meanings of R³,] is hydrogen, -CO-(C₁-C₇)-alkyl, -CO-(C₁-C₃)-alkylaryl or -CO-aryl,

R⁶ is -F, -OH, -O-(C₁-C₁₀)-alkyl, -O-phenyl, -O-CO-(C₁-C₁₀)-alkyl, -O-CO-aryl, -NR⁸R⁹, oxo, phenyl, -CO-(C₁-C₅)-alkyl, -CF₃, -CN, -CONR⁸R⁹, -COOH, -CO-O-(C₁-C₅)-alkyl, -CO-O-aryl, -S(O)_n-(C₁-C₅)-alkyl, or -SO₂-NR⁸R⁹,

R⁷ [has, independently of R⁶, one of the meanings of R⁶,] is -F, -OH, -O-(C₁-C₁₀)-alkyl, -O-phenyl, -O-CO-(C₁-C₁₀)-alkyl, -O-CO-aryl, -NR⁸R⁹, oxo, phenyl, -CO-(C₁-C₅)-alkyl, -CF₃, -CN, -CONR⁸R⁹, -COOH, -CO-O-(C₁-C₅)-alkyl, -CO-O-aryl, -S(O)_n-(C₁-C₅)-alkyl, or -SO₂-NR⁸R⁹,

R⁸ is hydrogen or (C₁-C₅)-alkyl, and

R⁹ is hydrogen, (C₁-C₅)-alkyl or phenyl,

wherein each aryl group is chosen from phenyl, naphthyl [or] and heteroaryl groups,

wherein said phenyl, naphthyl and heteroaryl groups are unsubstituted groups or substituted groups which are substituted by at least one substituent chosen from [all of which may be substituted by one or more identical or different substituents from the series] halogen, (C₁-C₅)-alkyl or phenyl, -OH, -O-(C₁-C₅)-alkyl, (C₁-C₂)-alkylenedioxy, -N⁸R⁹, -NO₂, -CO-(C₁-C₅)-alkyl, -CF₃, -CN, -CONR⁸R⁹, -COOH, -CO-O-(C₁-C₅)-alkyl, -S(O)_n-(C₁-C₅)-alkyl, and -SO₂-NR⁸R⁹,

wherein said heteroaryl groups are [is a] 5- to 7-membered unsaturated heterocycles [which contains one or more] comprising at least one heteroatom chosen from [the series] O, N, and S, and

wherein n is 0, 1 or 2,

or a physiologically acceptable salt, hydrate, or ester thereof, in any stereoisomeric or tautomeric form, or a mixture of any such compounds in any ratio. [in all its stereoisomeric and tautomeric forms and mixtures thereof in all ratios, and its physiologically acceptable salts, hydrates and esters.]

3. (Amended) The compound as claimed in claim 1 [Compound of the formula I as claimed in claim 1], in which

R¹ is hydrogen, unsubstituted (C₂-C₄)-alkyl, substituted (C₂-C₄)-alkyl which [may be] is substituted by [one or more substituents] at least one R⁶, or (C₁-C₂)-alkylaryl,

R² is unsubstituted (C₂-C₄)-alkyl, substituted (C₂-C₄)-alkyl which [may be] is substituted by [one or more substituents] at least one R⁶, [or] cyclohexylmethyl or (C₁-C₂)-alkylaryl,

or R¹ and R² [form], together with the nitrogen atom bearing them, form a 5-7-membered ring [which optionally contains no or another] wherein said 5-7-membered ring optionally comprises an additional heteroatom chosen from [the series] N, O, and S,

R³ is hydrogen, -CO-(C₁-C₃)-alkyl or -CO-aryl,

R⁴ is aryl, (C₁-C₅)-alkyl or -CO-O-aryl, **wherein R⁴ is unsubstituted or substituted with at least one substituent chosen from [each of which may be substituted by one or more substituents] R⁷,**

R⁵ is hydrogen,

R⁶ is -OH, -O-(C₁-C₃)-alkyl, -NR⁸R⁹ or -COOH, **and**

R⁷ is -OH, (C₁-C₁₀)-alkyloxy, phenoxy or oxo,

wherein each aryl group is chosen from phenyl, thienyl, furyl [or] **and** pyridyl,

wherein said phenyl, thienyl, furyl and pyridyl groups are unsubstituted groups or substituted groups which are substituted by at least one substituent chosen from [each of which may be substituted by one or more substituents from the series] (C₁-C₃)-alkyl, halogen, (C₁-C₃)-alkyloxy and (C₁-C₂)-alkylenedioxy, [and]

[R⁸ and R⁹ have the meanings stated in claim 1],

or a physiologically acceptable salt, hydrate, or ester thereof, in any stereoisomeric or tautomeric form, or a mixture of any such compounds in any ratio. [in all its stereoisomeric and tautomeric forms and mixtures thereof in all ratios, and its physiologically acceptable salts, hydrates and esters.]

4. (Amended) **The compound as claimed in claim 1** [Compounds of the formula I as claimed in claim 1], in which

R¹ is arylmethyl, [and]

R² is arylmethyl or cyclohexylmethyl,

or R¹ and R² [form], together with the nitrogen atom bearing them, **form** a pyrrolidine, piperidine, morpholine, dimethylmorpholine, thiomorpholine, or N-(C₁-C₂)-alkylpiperazine ring,

R³ is hydrogen,

R⁴ is alkyl or 1,2-dihydroxypropyl,

R⁵ is hydrogen,

R⁶ is -OH, -O-(C₁-C₃)-alkyl, -NR⁸R⁹ or -COOH, **and**

R⁷ is -OH, decyloxy [and] **or** phenoxy,

wherein each aryl group is chosen from unsubstituted phenyl or substituted phenyl, which is substituted by at least one substituent chosen from [which may be substituted by one or more substituents from the series] (C₁-C₃)-alkyl, halogen and (C₁-C₃)-alkyloxy and (C₁-C₂)-alkylenedioxy, [and]

[R⁸ and R⁹ have the meanings stated in claim 1.]

or a physiologically acceptable salt, hydrate, or ester thereof, in any stereoisomeric or tautomeric form, or a mixture of any such compounds in any ratio. [in all its stereoisomeric and tautomeric forms and mixtures thereof in all ratios, and its physiologically acceptable salts, hydrates and esters.]

5. (Amended) The compound as claimed in claim 1 [Compounds of the formula I as claimed in claim 1], which is a tetrahydropteridine [in which] wherein R^4 is aryl, (C_1-C_5) -alkyl or $-CO-O$ -aryl, and wherein said R^4 is unsubstituted or substituted with at least one substituent chosen from R^7 . [each of which may be substituted by one or more substituents R^7 .]

6. (Amended) The compound as claimed in claim 1 [Compounds of the formula I as claimed in claim 1], which is a pteridine [in which] wherein

R^1 and R^2 are each, independently alkyl or [and/or] aryl, or

[in which] R^1 is hydrogen and R^2 is cycloalkyl or cycloalkylalkyl, and

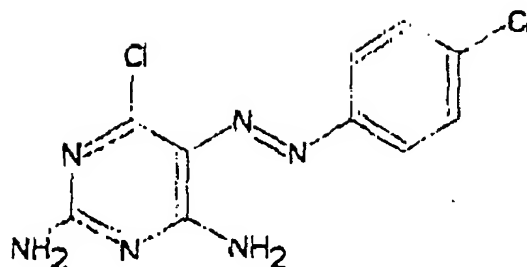
[in which] wherein R^4 is aryl, (C_1-C_5) -alkyl or $-CO-O$ -aryl, wherein said R^4 is unsubstituted or substituted with at least one substituent chosen from R^7 . [each of which may be substituted by one or more substituents R^7 .]

7. (Amended) A pharmaceutical comprising at least one of the compounds as claimed in claim 1 [a compound of the formula I as claimed in claim 1 in addition to] and at least one additional ingredient chosen from conventional excipients [and] additives and [optionally] further active ingredients.

8. (Amended) [A pharmaceutical as claimed in claim 7 for the therapy and prophylaxis of] A method of treating or preventing strokes, pathological falls in blood pressure, [in particular in septic shock and in cancer therapy with cytokines,] ulcerative colitis, transplant rejection reactions, nephritis, reperfusion damage, infarct damage, cardiomyopathy, Alzheimer's disease, epilepsy, migraine or [and] neuritis of varying etiogenesis comprising administration of at least one pharmaceutical of claim 7 to a patient in need thereof.

9. (Amended) [A pharmaceutical as claimed in claim 7 as] A method of inhibiting [inhibitor of] NO synthase comprising administration of at least one pharmaceutical of claim 7 to a patient in need thereof.

11. (Amended) A process for preparing the compound as claimed in claim 1 comprising [a compound of the formula I as claimed in claim 1, by] reacting a compound of [the] formula II



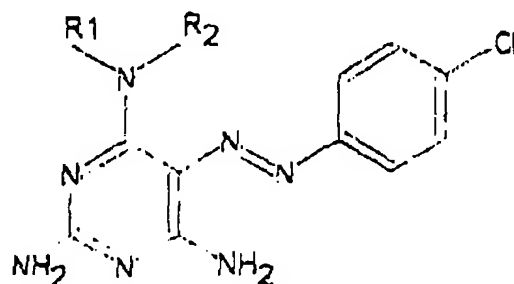
(II)

with a compound of [the] formula III



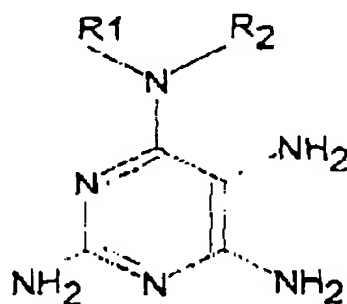
(III)

[to give a] which results in a compound of [the] formula IV



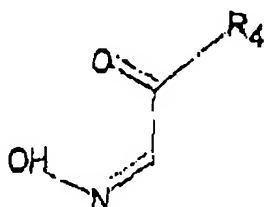
(IV)

[and converting the latter by] wherein the compound of formula IV is converted to a compound of formula V by catalytic hydrogenation [into a compound of the formula V]



(V)

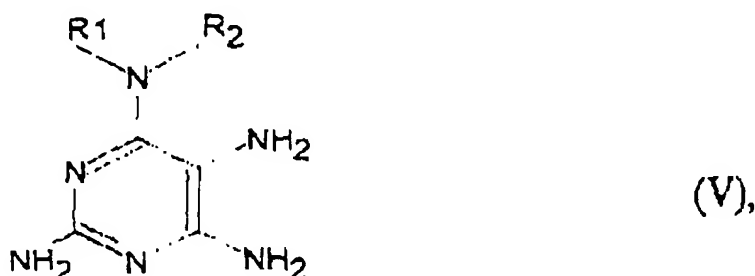
and wherein a compound of formula V [which] is reacted with a compound of the formula VI



(VI)

to give a compound of formula I [which can be converted by suitable derivatization, preferably acylation, into the desired compound of the formula I or its physiologically acceptable salts, hydrates, esters and adducts, and in which the substituents have the meanings stated in claims 1 to 3].

12. (Amended) A compound of the formula V



in which

R^1 [has the meaning defined in claim 1, and] is hydrogen, C_1 - C_{20} -alkyl, C_2 - C_{20} -alkenyl, C_2 - C_{20} -alkynyl, cycloalkyl with three to eight ring carbon atoms, cycloalkenyl with three to eight ring carbon atoms, cycloalkylalkyl with five to six ring carbon atoms, aryl, alkylaryl or arylalkyl, wherein R^1 is unsubstituted or substituted with at least one substituent chosen from R^6 ,

R^2 is [independently of R^1] C_1 - C_{20} -alkyl, C_2 - C_{20} -alkenyl, C_2 - C_{20} -alkynyl, cycloalkyl with three to eight ring carbon atoms, cycloalkenyl with three to eight ring carbon atoms, [or] cycloalkylalkyl with five to six ring carbon atoms, aryl, alkylaryl or arylalkyl, wherein R^1 is unsubstituted or substituted with at least one substituent chosen from R^6 [where the organic radicals may be substituted by one or more substituents R^6],

or R^1 and R^2 [may], together with the nitrogen atom bearing them, form a 3-8-membered ring [which may], wherein said 3-8 membered ring optionally comprises [contains] 0, 1 or 2 further heteroatoms chosen from [the series] N, O, and S and [which is optionally substituted by one or more radicals R^6] wherein said 3-8-membered ring is unsubstituted or substituted by at least one substituent chosen from R^6 , and

R^6 [has the meaning defined in claim 1] is -F, -OH, -O-(C_1 - C_{10})-alkyl, -O-phenyl, -O-CO-(C_1 - C_{10})-alkyl, -O-CO-aryl, -NR⁸R⁹, oxo, phenyl, -CO-(C_1 - C_5)-alkyl, -CF₃, -CN, -CONR⁸R⁹, -COOH, -CO-O-(C_1 - C_5)-alkyl, -CO-O-aryl, -S(O)_n-(C_1 - C_5)-alkyl, or -SO₂-NR⁸R⁹

R^8 is hydrogen or C_1 - C_{20} -alkyl, and

R^9 is hydrogen, C_1 - C_{20} -alkyl or aryl,

or a physiologically acceptable salt, hydrate, or ester thereof, in any stereoisomeric or tautomeric form, or a mixture of any such compounds in any ratio..